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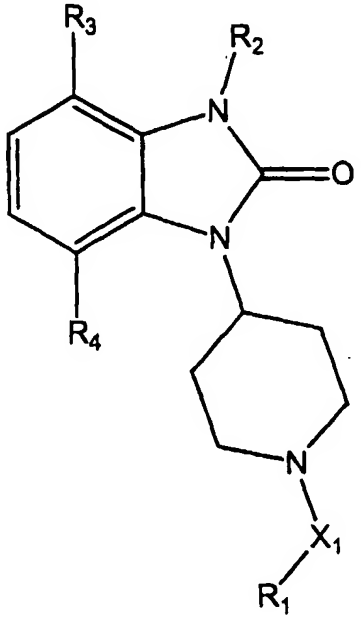
(54) Title: BENZIMIDAZOLE COMPOUNDS HAVING NOCICEPTIN RECEPTOR AFFINITY



(I)

(57) Abstract: Disclosed are compounds of formula (I), wherein A, R_1, R_2, R_3, R_4 and X_1 are as disclosed herein. The compounds have affinity for the ORL1 receptor and are useful in the treatment of chronic and acute pain.

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BENZIMIDAZOLE COMPOUNDS HAVING NOCICEPTIN RECEPTOR AFFINITY

This application claims the benefit of U.S. provisional no. 60/169,394 filed December 6, 1999. the disclosure of which is hereby incorporated by reference

BACKGROUND OF THE INVENTION

Chronic pain is a major contributor to disability in the industrialized world and is the cause of an untold amount of suffering. The successful treatment of severe and chronic pain is a primary goal of the physician with opioid analgesics being the current drugs of choice. Unfortunately, this class of compounds produces several undesirable side effects including respiratory depression, constipation, and the development of tolerance and dependence.

Opioids are derived from the opium poppy *papaya somniferum* and include drugs such as morphine, codeine and semi-synthetic compounds derived from them and from thebaine, another component of the opium poppy. It was hypothesized that the opioids derived their therapeutic effect by interacting with specific receptor sites in the body. Later experiments led to the belief that there were more than one receptor site in the body, in explanation for the fact that the synthetic compound nalorphine provides analgesic activity while at the same time, antagonizes the analgesic effect of morphine.

Until recently, there was evidence of three major classes of opioid receptors in the central nervous system (CNS), with each class having subtype receptors. These receptor classes were designated as μ, δ and k. As opiates had a high affinity to these receptors while not being endogenous to the body, research followed in order to identify and isolate the endogenous ligands to these receptors. These ligands were identified as enkephalins, endorphins and dynorphins.

Recent experimentation has led to the identification of a cDNA encoding an opioid receptor-like (ORL1) receptor with a high degree of homology to the known receptor classes. This newly discovered receptor was classified as an opioid receptor based only on structural grounds, as the receptor did not exhibit pharmacological homology. It was initially demonstrated that non-selective ligands having a high affinity for μ, δ and k receptors had low affinity for the ORL1. This characteristic, along with the fact that an endogenous ligand had not yet been discovered, led to the term "orphan receptor".

Subsequent research led to the isolation and structure of the endogenous ligand of the ORL1 receptor. This ligand is a seventeen amino acid peptide structurally similar to members of the opioid peptide family

The discovery of the ORL1 receptor presents an opportunity in drug discovery for novel compounds which can be administered for pain management or other syndromes modulated by this receptor.

Given the close structural homology of ligands to the ORL1 receptor to ligands of the other opioid receptors, such drug discovery could also lead to compounds having a higher affinity for the μ, δ and k receptors than known compounds, while producing less side effects.

OBJECTS AND SUMMARY OF THE INVENTION

It is accordingly an object of the present invention to provide new compounds which exhibit affinity for the ORL1 receptor.

It is another object of the present invention to provide new compounds which exhibit affinity for the ORL1 receptor and one or more of the μ, δ or k receptors.

It is another object of the present invention to provide new compounds for treating a patient suffering from chronic or acute pain by administering a compound having affinity for the ORL1 receptor.

It is another object of the invention to provide new compounds which have agonist activity at the μ, δ and k receptors which is greater than compounds currently available e.g. morphine.

It is another object of the invention to provide methods of treating chronic and acute pain by administering compounds which have agonist activity at the μ, δ and k receptors which is greater than compounds currently available.

It is another object of the invention to provide methods of treating chronic and acute pain by administering non-opioid compounds which have agonist activity at the μ, δ and k receptors and which produce less side effects than compounds currently available.

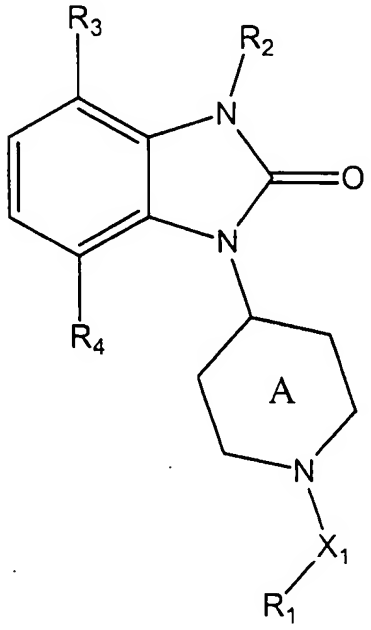
It is another object of the present invention to provide compounds useful as analgesics, antiinflammatories, diuretics, anesthetics and neuroprotective agents and methods for administering said compounds.

It is another object of the present invention to provide a method of modulating a response from opioid receptors comprising administering a compound having a binding

affinity for the ORL1 receptor of less than 500 K_i (nM) and a binding affinity for the mu receptor of less than 25 K_i (nM).

It is another object of the invention to provide a method of reducing side effects associated with the administration of opioid analgesics in a human patient comprising administering to a human patient an analgesically effective amount of a non-opioid compound which exhibits a binding affinity for the ORL1 receptor of less than 500 K_i (nM). In other embodiments, the compound has a binding affinity for the mu receptor of less than 25 K_i (nM).

Other objects and advantages of the present invention will become apparent from the following detailed description thereof. With the above and other objects in view, the present invention in certain embodiments comprises compounds having the general formula (I):



(I)

wherein

A is a saturated, unsaturated or partially unsaturated ring

X_1 is selected from the group consisting of a bond, C_{1-10} branched or straight alkyl, alkenyl, alkynylene optionally substituted with 1-3 halogen, oxo or phenyl groups, said phenyl group optionally substituted with 1-3 halogen or C_{1-10} alkyl groups;

R_1 is selected from the group consisting of hydrogen, C_{3-12} cycloalkyl, C_{3-12} cycloalkenyl, a monocyclic, bicyclic or tricyclic aryl or heteroaryl ring, a heteromonocyclic ring, and a heterobicyclic ring system, wherein said C_{3-12} cycloalkyl, C_{3-12} cycloalkenyl, monocyclic, bicyclic or tricyclic aryl or heteroaryl ring, heteromonocyclic ring, and

heterobicyclic ring system are optionally substituted with 1-3 substituents selected from the group consisting of halogen, C_{1-10} alkyl, nitro, trifluoromethyl, phenyl, benzyl, phenyloxy and benzyloxy, wherein said phenyl, benzyl, phenyloxy and benzyloxy are optionally substituted with halogen or C_{1-10} alkyl;

R_2 is selected from the group consisting of C_{1-10} alkyl, C_{3-12} cycloalkyl and halogen, said alkyl and cycloalkyl substituted with an oxo group; and

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, C_{1-3} alkyl, C_{1-3}alkoxy, C_{1-3} carbonyl and halogen; and pharmaceutically acceptable salts thereof.

In preferred embodiments, A has one double bond at the 1,2 position.

In preferred embodiments, X_1R_1 is not hydrogen.

In preferred embodiments, A has one double bond at the 1,2 position.

In other preferred embodiments X_1 is selected from a bond, methyl, ethyl or propyl.

In other preferred embodiments X_1 is substituted with fluorophenyl.

In other preferred embodiments R_1 is a tricyclic aryl ring, preferably dibenzocycloheptyl.

In other preferred embodiments R_1 is a cycloalkyl, preferably cyclopentyl, cyclohexyl or cycloheptyl, wherein the cycloalkyl is optionally substituted with a C_{1-3} alkyl.

In other preferred embodiments R_1 is a monocyclic aryl ring, preferably phenyl, wherein the aryl ring is optionally substituted with a halogen, C_{1-3} alkyl, phenyl or benzyloxy.

In other preferred embodiments, R_1 is selected from napthyl, benzyloxyphenyl, decahydronaphyl, 1,3 hydro-indene, propylhexane, cyclodecyl, biphenylmethyl, phenylethyl, cyclooctyl, 1,2,3,4,hydro-napthyl, 1-3 dimethyl-pentyl.

In other preferred embodiments, R_2 is a methyl, ethyl or propyl wherein the methyl ethyl and propyl are optionally substituted with an oxo group.

In other preferred embodiments, R_3 and R_4 are both hydrogen.

As used herein, the term "alkyl" means a linear or branched saturated aliphatic hydrocarbon group having a single radical and 1-10 carbon atoms. Examples of alkyl groups include methyl, propyl, isopropyl, butyl, n-butyl, isobutyl, sec-butyl, tert-butyl, and pentyl. A branched alkyl means that one or more alkyl groups such as methyl, ethyl or propyl, replace one or both hydrogens in a $-CH_2-$ group of a linear alkyl chain.

The term "cycloalkyl" means a non-aromatic mono- or multicyclic hydrocarbon ring system having a single radical and 3-12 carbon atoms. Exemplary monocyclic cycloalkyl

rings include cyclopropyl, cyclopentyl, and cyclohexyl. Exemplary multicyclic cycloalkyl rings include adamantyl and norbornyl.

The term "alkenyl" means a linear or branched aliphatic hydrocarbon group containing a carbon-carbon double bond having a single radical and 2-10 carbon atoms. A "branched" alkenyl means that one or more alkyl groups such as methyl, ethyl or propyl replace one or both hydrogens in a $-CH_2-$ or -CH= linear alkenyl chain. Exemplary alkenyl groups include ethenyl, 1- and 2- propenyl, 1-, 2- and 3- butenyl, 3-methylbut-2-enyl, 2-propenyl, heptenyl, octenyl and decenyl.

The term "cycloalkenyl" means a non-aromatic monocyclic or multicyclic hydrocarbon ring system containing a carbon-carbon double bond having a single radical and 3 to 12 carbon atoms. Exemplary monocyclic cycloalkenyl rings include cyclopropenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl. An exemplary multicyclic cycloalkenyl ring is norbornenyl.

The term "aryl" means a carbocyclic aromatic ring system containing one, two or three rings which may be attached together in a pendent manner or fused, and containing a single radical. Exemplary aryl groups include phenyl and naphthyl.

The term "heterocyclic" means cyclic compounds having one or more heteroatoms (atoms other than carbon) in the ring, and having a single radical. The ring may be saturated, partially saturated and unsaturated, and the heteroatoms may be selected from the group consisting of nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include saturated 3 to 6- membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, such as pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl; saturated 3- to 6-membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as morpholinyl; saturated 3- to 6- membered heteromonocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, such as thiazolidinyl. Examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, and dihydrofuran.

The term "heteroaryl" means unsaturated heterocyclic radicals, wherein heterocyclic is as previously described. Exemplary heteroaryl groups include unsaturated 3 to 6 membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, such as pyrrolyl, pyridyl, pyrimidyl, and pyrazinyl; unsaturated condensed heterocyclic groups containing 1 to 5 nitrogen atoms, such as indolyl, quinolyl, isoquinolyl; unsaturated 3 to 6- membered heteromonocyclic groups containing an oxygen atom, such as furyl; unsaturated 3 to 6

membered heteromonocyclic groups containing a sulfur atom, such as thienyl; unsaturated 3 to 6 membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as oxazolyl; unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as benzoxazolyl; unsaturated 3 to 6 membered heteromonocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, such as thiazolyl; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, such as benzothiazolyl. The term "heteroaryl" also includes unsaturated heterocyclic radicals, wherein heterocyclic is as previously described, in which the heterocyclic group is fused with an aryl group, in which aryl is as previously described. Exemplary fused radicals include benzofuran, benzdioxole and benzothiophene.

As used herein, the term "patient" includes both human and other mammals.

As used herein, the term "halogen" includes fluoride, bromide, chloride, iodide or alabamide.

The invention disclosed herein is meant to encompass all pharmaceutically acceptable salts thereof of the disclosed compounds. The pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salt, potassium salt, secium salt and the like; alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the like; inorganic acid salts such as hydrochloride, hydrobromide, sulfate, phosphate and the like; organic acid salts such as formate, acetate, trifluoroacetate, maleate, tartrate and the like; sulfonates such as methanesulfonate, benzenesulfonate, p-toluenesulfonate, and the like; amino acid salts such as arginate, asparginate, glutamate and the like.

The invention disclosed herein is also meant to encompass all prodrugs of the disclosed compounds. Prodrugs are considered to be any covalently bonded carriers which release the active parent drug in vivo.

The invention disclosed herein is also meant to encompass the in vivo metabolic products of the disclosed compounds. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled compound of the invention, administering

it parenterally in a detectable dose to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur and isolating its conversion products from the urine, blood or other biological samples.

The invention disclosed herein is also meant to encompass the disclosed compounds being isotopically-labelled by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Some of the compounds disclosed herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present invention is also meant to encompass all such possible forms as well as their racemic and resolved forms and mixtures thereof. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended to include both E and Z geometric isomers. All tautomers are intended to be encompassed by the present invention as well

As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

The term "chiral center" refers to a carbon atom to which four different groups are attached.

The term "enantiomer" or "enantiomeric" refers to a molecule that is nonsuperimposeable on its mirror image and hence optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image rotates the plane of polarized light in the opposite direction.

The term "racemic" refers to a mixture of equal parts of enantiomers and which is optically inactive.

The term "resolution" refers to the separation or concentration or depletion of one of the two enantiomeric forms of a molecule.

Certain preferred compounds of formula I according to the invention include: 1-[1-dibenzocycloheptyl-4-piperidinyl]- 3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(4-propylcyclohexane)-4-piperidinyl]- 3-[1-oxo-propyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(4-propylcyclohexane)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(4-propylcyclohexane)-4-piperidinyl]- 3-[2-oxo-cyclopropyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(4-propyl-1,2-cyclohexene)-4-piperidinyl-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(4,4-difluorophenylbutyl)-4-piperidinyl]- 3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one; and

1-[1-(4-phenyl-phenylmethyl)-4-piperidinyl]- 3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one.

1-[1-(2-napthyl-methyl)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(4-benzyloxy-benzyl)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(decahydronaphyl)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(2[1,3 dihydro-indene])-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(4-isopropylhexane)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(4-[1-methyl-ethyl]hexane)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-cyclodecyl -4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(3-diphenylpropyl)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(2- phenylethyl)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(cyclooctylmethyl)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(4-[1,2,3,4,hydro-napthyl])-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(4-[1-3 dimethyl-pentyl])-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one; and pharmaceutically acceptable salts thereof..

The present invention is also directed to the following compounds:
1-[4-dibenzocycloheptyl-4-piperidinyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;
1-[4-(4-propylcyclohexane)-4-piperidinyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;
1-[4-(4-propyl-1,2-cyclohexene)-4-piperidinyl-1,3-dihydro-2H-1,3-benzamidazol-2-one;
1-[4-(4,4-difluorophenylbutyl)-4-piperidinyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;
1-[4-(4-phenyl-phenylmethyl)-4-piperidinyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one; and pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention can be administered to anyone requiring modulation of the opioid and ORL1 receptors. Administration may be orally, topically, by suppository, inhalation, or parenterally.

The present invention also encompasses all pharmaceutically acceptable salts of the foregoing compounds. One skilled in the art will recognize that acid addition salts of the presently claimed compounds may be prepared by reaction of the compounds with the appropriate acid via a variety of known methods.

Various oral dosage forms can be used, including such solid forms as tablets, gelcaps, capsules, caplets, granules, lozenges and bulk powders and liquid forms such as emulsions, solution and suspensions. The compounds of the present invention can be administered alone or can be combined with various pharmaceutically acceptable carriers and excipients known to those skilled in the art, including but not limited to diluents, suspending agents, solubilizers, binders, disintegrants, preservatives, coloring agents, lubricants and the like.

When the compounds of the present invention are incorporated into oral tablets, such tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, multiply compressed or multiply layered. Liquid oral dosage forms include aqueous and nonaqueous solutions, emulsions, suspensions, and solutions and/or suspensions reconstituted from non-effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, coloring agents, and flavoring agents. When the compounds of the present invention are to be injected parenterally, they may be, e.g., in the form of an isotonic sterile solution. Alternatively, when the compounds of the present

invention are to be inhaled, they may be formulated into a dry aerosol or may be formulated into an aqueous or partially aqueous solution.

In addition, when the compounds of the present invention are incorporated into oral dosage forms, it is contemplated that such dosage forms may provide an immediate release of the compound in the gastrointestinal tract, or alternatively may provide a controlled and/or sustained release through the gastrointestinal tract. A wide variety of controlled and/or sustained release formulations are well known to those skilled in the art, and are contemplated for use in connection with the formulations of the present invention. The controlled and/or sustained release may be provided by, e.g., a coating on the oral dosage form or by incorporating the compound(s) of the invention into a controlled and/or sustained release matrix.

Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms, are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986), incorporated by reference herein. Techniques and compositions for making solid oral dosage forms are described in Pharmaceutical Dosage Forms: Tablets (Lieberman, Lachman and Schwartz, editors) 2nd edition, published by Marcel Dekker, Inc., incorporated by reference herein. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are also described in Remington's Pharmaceutical Sciences (Arthur Osol, editor), 1553B1593 (1980), incorporated herein by reference. Techniques and composition for making liquid oral dosage forms are described in Pharmaceutical Dosage Forms: Disperse Systems, (Lieberman, Rieger and Banker, editors) published by Marcel Dekker, Inc., incorporated herein by reference.

When the compounds of the present invention are incorporated for parenteral administration by injection (e.g., continuous infusion or bolus injection), the formulation for parenteral administration may be in the form of suspensions, solutions, emulsions in oily or aqueous vehicles, and such formulations may further comprise pharmaceutically necessary additives such as stabilizing agents, suspending agents, dispersing agents, and the like. The compounds of the invention may also be in the form of a powder for reconstitution as an injectable formulation.

The dose of the compounds of the present invention is dependent upon the affliction to be treated, the severity of the symptoms, the route of administration, the frequency of the

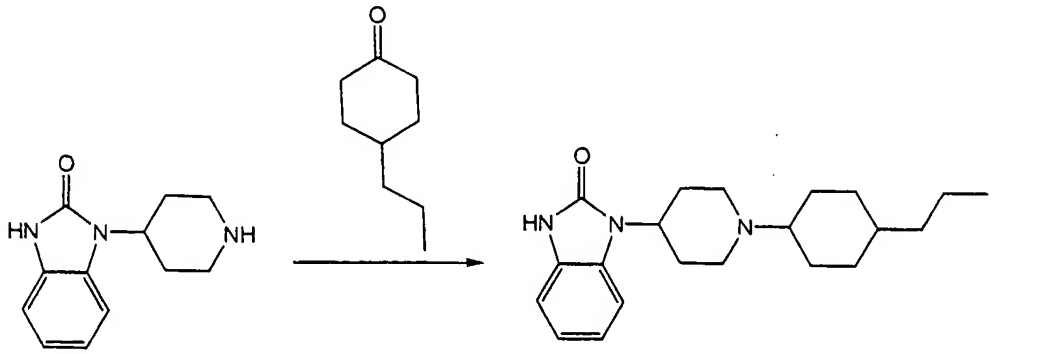
dosage interval, the presence of any deleterious side-effects, and the particular compound utilized, among other things.

The following examples illustrate various aspects of the present invention, and are not to be construed to limit the claims in any manner whatsoever.

Example 1

1-[4-(4-propylcyclohexane)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one.

The above compound was synthesized according to the following synthetic scheme and general procedure:



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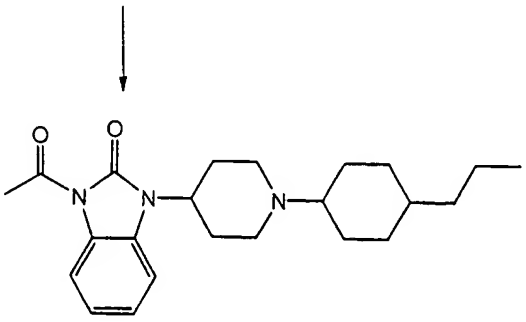

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General Procedure for Reductive Coupling. A solution containing the amine and ketone in toluene was refluxed in the presence of molecular sieves for 5-6 hours. The reaction mixture was cooled and filtered through Celite and the Celite cake was washed with Dichloromethane. The combined filtrate was concentrated to dryness. The residue was dissolved in a mixture of THF and methanol(10:1). To the solution was then added 1 eq of

NaCNBH3 in one portion and a few drops of acetic acid to adjust pH=4-5. The reaction was stirred at room temperature for 12 hours. The reaction mixture was diluted with EtOAc and washed with 1N NaOH solution. The aqueous was extracted with additional EtOAc and the combined organic was dried with MgSO4, filtered and concentrated. The desired product was purified either by recrystalization or flash chromatography on silica gel.

Preparation of Example 1

To a solution of 380 mg of example 1 in 10 ml dichloromethane was added 236 mg Et_3N, 99 mg acetyl chloride and a catalytic amount of DMAP. The reaction was stirred at room temperature for 12 hours. After diluting with dichloromethane the mixture was washed with brine and the aqueous phase extracted with additional dichloromethane. The combined organic extracts were dried over MgSO4, filtered and concentrated. The residue was purified via flash chromatography(silica, EtOAc) to give desired product.
1HNMR in $CDCl_3$(ppm): 7.35 (t, 2H), 7.10 (m, 7H), 5.05 (s, 2H), 3.13-2.80 (m, 9H), 2.62 (s, 3H), 2.40 (m, 2H), 2.13 (m, 1H), 1.89 (bd, 2H), 1.70 (m, 1H). LCMS: 404(M+1).

The general procedures disclosed above can be modified in order to synthesize the other preferred compounds of the invention.

Example 2

Nociceptin affinity at the ORL1 receptor for preferred compounds was obtained using the following assay:

Membranes from recombinant HEK-293 cells expressing the human opioid receptor-like receptor (ORL-1) (Receptor Biology) were prepared by lysing cells in ice-cold hypotonic buffer (2.5 mM $MgCl_2$, 50 mM HEPES, pH 7.4) (10 ml/10 cm dish) followed by homogenization with a tissue grinder/teflon pestle. Membranes were collected by centrifugation at 30,000 x g for 15 min at 4°C and pellets resuspended in hypotonic buffer to a final concentration of 1-3 mg/ml. Protein concentrations were determined using the BioRad protein assay reagent with bovine serum albumen as standard. Aliquots of the ORL-1 receptor membranes were stored at –80°C.

Functional SGTPγS binding assays were conducted as follows. ORL-1 membrane solution was prepared by sequentially adding final concentrations of 0.066 μg/μl ORL-1 membrane protein, 10 μg/ml saponin, 3 μM GDP and 0.20 nM [^{35}S]GTPγS to binding buffer (100 mM NaCl, 10 mM $MgCl_2$, 20 mM HEPES, pH 7.4) on ice. The prepared membrane

solution (190 µl/well) was transferred to 96-shallow well polypropylene plates containing 10 µl of 20x concentrated stock solutions of agonist prepared in DMSO. Plates were incubated for 30 min at room temperature with shaking. Reactions were terminated by rapid filtration onto 96-well Unifilter GF/B filter plates (Packard) using a 96-well tissue harvester (Brandel) and followed by three filtration washes with 200 µl ice-cold binding buffer (10 mM NaH_2PO_4, 10 mM Na_2HPO_4, pH 7.4). Filter plates were subsequently dried at 50°C for 2-3 hours. Fifty µl/well scintillation cocktail (BetaScint; Wallac) was added and plates were counted in a Packard Top-Count for 1 min/well.

Data was analyzed using the curve fitting functions in GraphPad PRISM™, v. 3.0 and the results are set forth in table 1 below:

TABLE 1

Nociceptin Affinity

Compound	**calc K_i (nM)**
1-[4-(4-propylcyclohexane)-4-piperidinyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one	394
1-[4-(4-propylcyclohexane)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one	464
1-[4-(4-propylcyclohexane)-4-piperidinyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one	166
1-[4-(4-propyl-1,2-cyclohexene)-4-piperidinyl-1,3-dihydro-2H-1,3-benzamidazol-2-one	469
1-[4-(4,4-difluorophenylbutyl)-4-piperidinyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one	420
1-[4-(4-phenyl-phenylmethyl)-4-piperidinyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one	1252

Example 3

Affinity at the μ, k and δ receptors for preferred compounds was obtained according to the following assays:

Mu, kappa or delta opioid receptor membrane solution was prepared by sequentially adding final concentrations of 0.075 μg/μl of the desired membrane protein, 10 μg/ml saponin, 3 μM GDP and 0.20 nM [^{35}S]GTPγS to binding buffer (100 mM NaCl, 10 mM $MgCl_2$, 20 mM HEPES, pH 7.4) on ice. The prepared membrane solution (190 μl/well) was transferred to 96-shallow well polypropylene plates containing 10 μl of 20x concentrated stock solutions of agonist prepared in DMSO. Plates were incubated for 30 min at room temperature with shaking. Reactions were terminated by rapid filtration onto 96-well Unifilter GF/B filter plates (Packard) using a 96-well tissue harvester (Brandel) and followed by three filtration washes with 200 μl ice-cold binding buffer (10 mM NaH_2PO_4, 10 mM Na_2HPO_4, pH 7.4). Filter plates were subsequently dried at 50°C for 2-3 hours. Fifty μl/well scintillation cocktail (MicroScint20, Packard) was added and plates were counted in a Packard Top-Count for 1 min/well.

Data were analyzed using the curve fitting functions in GraphPad PRISM™, v. 3.0 and the results are set forth in table 2 below:

TABLE 2

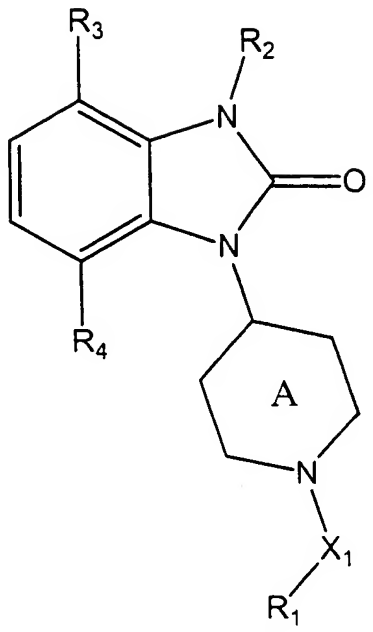
	calc K_i (nM)		
Compound	**μ**	**k**	**δ_2**
1-[4-(4-propylcyclohexane)-4-piperidinyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one	19	270	>10,000
1-[4-(4-propylcyclohexane)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one	23.2	1600	>10,000
1-[4-(4-propylcyclohexane)-4-piperidinyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one	457	940	2210
1-[4-(4-propyl-1,2-cyclohexene)-4-piperidinyl-1,3-dihydro-2H-1,3-benzamidazol-2-one	265	1500	1220

TABLE 2

	calc K_i (nM)		
Compound	**μ**	**k**	**δ_2**
1-[4-(4,4-difluorophenylbutyl)-4-piperidinyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one	52	1200	2050
1-[4-(4-phenyl-phenylmethyl)-4-piperidinyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one	105	1300	3290

What is claimed is:

1. A compound of the formula (I):



(I)

wherein

A is a saturated, unsaturated or partially unsaturated ring

X_1 is selected from the group consisting of a bond, C_{1-10} branched or straight alkyl, alkenyl, alkynylene optionally substituted with 1-3 halogen, oxo or phenyl groups, said phenyl group optionally substituted with 1-3 halogen or C_{1-10} alkyl groups;

R_1 is selected from the group consisting of hydrogen, C_{3-12} cycloalkyl, C_{3-12} cycloalkenyl, a monocyclic, bicyclic or tricyclic aryl or heteroaryl ring, a heteromonocyclic ring, and a heterobicyclic ring system, wherein said C_{3-12} cycloalkyl, C_{3-12} cycloalkenyl, monocyclic, bicyclic or tricyclic aryl or heteroaryl ring, heteromonocyclic ring, and heterobicyclic ring system are optionally substituted with 1-3 substituents selected from the group consisting of halogen, C_{1-10} alkyl, nitro, trifluoromethyl, phenyl, benzyl, phenyloxy and benzyloxy, wherein said phenyl, benzyl, phenyloxy and benzyloxy are optionally substituted with halogen or C_{1-10} alkyl;

R_2 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{3-12} cycloalkyl and halogen, said alkyl optionally substituted with an oxo group; and

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, C_{1-3} alkyl, C_{1-3}alkoxy, C_{1-3} carbonyl and halogen; and pharmaceutically acceptable salt thereof.

2. A compound of claim 1 wherein A has a double bond at the 1,2 position.

3. A compound of claim 1 wherein X_1 is selected from a bond, methyl, ethyl or propyl.

4. A compound of claim 1 wherein X_1 is methyl.

5. A compound of claim 1 wherein X_1 is substituted with fluorophenyl.

6. A compound of claim 1 wherein R_1 is a tricyclic aryl ring

7. A compound of claim 1 wherein R_1 is a cycloalkyl

8. A compound of claim 1 wherein R_1 is a monocyclic aryl ring, wherein the aryl ring is optionally substituted with a halogen, C_{1-3} alkyl, phenyl or benzyloxy.

9. A compound of claim 1 wherein R_1 is selected from napthyl, benzyloxyphenyl, decahydronaphyl, 1,3 hydro-indene, propylhexane, cyclodecyl, biphenylmethyl, phenylethyl, cyclooctyl, 1,2,3,4,hydro-napthyl, 1-3 dimethyl-pentyl.

10. A compound of claim 4 wherein R_1 is selected from napthyl, benzyloxyphenyl, decahydronaphyl, 1,3 hydro-indene, propylhexane, cyclodecyl, biphenylmethyl, phenylethyl, cyclooctyl, 1,2,3,4,hydro-napthyl, 1-3 dimethyl-pentyl.

11. A compound of claim 1 wherein R_3 and R_4 are both hydrogen.

12. A compound of claim 1 selected from 1-[1-dibenzocycloheptyl-4-piperidinyl]- 3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(4-propylcyclohexane)-4-piperidinyl]- 3-[1-oxo-propyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(4-propylcyclohexane)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(4-propylcyclohexane)-4-piperidinyl]- 3-[2-oxo-cyclopropyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(4-propyl-1,2-cyclohexene)-4-piperidinyl-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(4,4-difluorophenylbutyl)-4-piperidinyl]- 3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one; and

1-[1-(4-phenyl-phenylmethyl)-4-piperidinyl]- 3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one.

1-[1-(2-napthyl-methyl)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(4-benzyloxy-benzyl)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(decahydronaphyl)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(2[1,3 dihydro-indene])-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(4-isopropylhexane)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(4-[1-methyl-ethyl]hexane)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-cyclodecyl -4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(3-diphenylpropyl)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(2- phenylethyl)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(cyclooctylmethyl)-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;

1-[1-(4-[1,2,3,4,hydro-napthyl])-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;
1-[1-(4-[1-3 dimethyl-pentyl])-4-piperidinyl]-3-[1-oxo-ethyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one; and
pharmaceutically acceptable salts thereof.

13. A pharmaceutical composition comprising a compound of claim 1 and at least one pharmaceutically acceptable excipient.

14. A method of treating pain comprising administering to a patient in need thereof, an effective amount of a compound according to claim 1.

15. A method of modulating a pharmacological response from the ORL1 receptor comprising administering an effective amount of a compound according to claim 1.

16. A compound selected from the group consisting of
1-[4-dibenzocycloheptyl-4-piperidinyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;
1-[4-(4-propylcyclohexane)-4-piperidinyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;
1-[4-(4-propyl-1,2-cyclohexene)-4-piperidinyl-1,3-dihydro-2H-1,3-benzamidazol-2-one;
1-[4-(4,4-difluorophenylbutyl)-4-piperidinyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;
1-[4-(4-phenyl-phenylmethyl)-4-piperidinyl]-1,3-dihydro-2H-1,3-benzamidazol-2-one;
and pharmaceutically acceptable salts thereof.

17. A pharmaceutical composition comprising a compound of claim 16 and at least one pharmaceutically acceptable excipient.

18. A method of treating pain comprising administering to a patient in need thereof, an eff ective amount of a compound according to claim 16.

19. A method of modulating a pharmacological response from the ORL1 receptor comprising administering an effective amount of a compound according to claim 16.

20. A method of modulating a response from opioid receptors comprising administering a compound having a binding affinity for the ORL1 receptor of less than 500 K_i (nM) and a binding affinity for the mu receptor of less than 25 K_i (nM).

21. A method of reducing side effects associated with the administration of opioid analgesics in a human patient comprising administering to said human patient an analgesically effective amount of a non-opioid compound which exhibits a binding affinity for the ORL1 receptor of less than 500 K_i (nM).

22. The method of claim 21 wherein said compound has a binding affinity for the mu eceptor of less than 25 K_i (nM).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/33019

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61K 31/454; A61P 29/02; C07D 401/04
US CL :514/322; 546/199
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/322; 546/199

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/36421 A1 (PFIZER PHARMACEUTICALS, INC.) 22 July 1999, see entire document.	1(parts),3,5,7 and 9-18
X	US 4,329,353 A (STOKBROEKX et al) 11 May 1982, col. 24.	1(parts),3,5,7 and 9-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
09 JANUARY 2001

Date of mailing of the international search report
22 FEB 2001

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
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Authorized officer
Patricia L. Morris

TERRY J. DEY
PARALEGAL SPECIALIST
TECHNOLOGY CENTER 1600

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/33019

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1(parts), 2,4,6,8 and 19-21
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/33019

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE
2. Where no meaningful search could be carried out, specifically:

As the drafting of the claims is not clear and concise and encompass such an enormous amount of products, a complete search is not possible. Claims 19-21 are drawn to any and all unknown compounds that are known to have a binding affinity for the ORL1 receptor or that reduce side effects associated with administration of opioid analgesics. Claims 19-21 are not dependent upon claim 1. The considerably, long list of substituents with their often numerous and/or cascading significances makes the present application not meet the requirements set forth in PCT article 6 (Claims shall be clear and concise). Therefore, the search has been based on the first discernible invention wherein A is a piperidine ring, R1 is selected from the group consisting of hydrogen, (optionally substitued) C3-12 cycloalkyl or C3-12 cycloalkenyl, X1 is a bond, and R2-R4 as set forth in claim 1.